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SCIENTIFIC RESEARCH ON PAPAVER BRACTEATUM

No. 23

Report of the Fourth Working Group on Papaver bracteatum 1/

Rennes, France

17 - 21 May 1976

1/ This meeting was held with the financial support of the United Nations Fund for Drug Abuse Control.

GE. 76-6477

REPORT OF THE FOURTH WORKING GROUP ON PAPAVER BRACTEATUM

1. During recent years, considerable interest has developed in Papaver bracteatum as a known source of thebaine and thus, by conversion, of codeine[2]. Though at the present time world codeine supply and demand are approximately in balance, reserve stocks in some countries are insufficient to compensate for one poor crop year. Meanwhile, medicinal needs for codeine are increasing year by year. Sources of codeine other than Papaver somniferum would therefore be desirable and the United Nations is interested in P. bracteatum as one such source.

2. A collaborative research project on this poppy was initiated by the United Nations Narcotics Laboratory and investigations are being carried out in many countries. Working Groups of experts were held in Geneva (1972)[3], Teheran (1973)[4] and Beltsville, Md., USA (1974)[5].

3. The fourth Working Group of experts[6] was convened in France from 17 to 21 May 1976 with the financial support of the United Nations Fund for Drug Abuse Control. Facilities for the meeting were provided at the Station d'Amélioration des Plantes near Rennes through the courtesy of the Director, Dr. J. Morice. The final discussions on 21 May 1976 were held at UNESCO Headquarters in Paris.

2/ Codeine is the most widely used anti-tussive and it is also extensively used as a mild analgesic. At present, codeine is mostly derived by the process of methylation from the morphine obtained from the opium poppy and about 90 per cent of legally produced morphine is converted into codeine.

3/ See report, document ST/SOA/SER.J/1.

4/ See report, document ST/SOA/SER.J/2.

5/ See report, document ST/SOA/SER.J/15.

6/ The list of participants and observers is given in Annex I.

4. The meeting was opened by Mr. M. Hives, Chief of the Plant Improvement Department of the French National Institute of Agronomic Research who welcomed the Group and stressed the importance of the research being carried out on P. bracteatum.

5. Dr. J. Morice was elected Chairman by acclamation. Dr. O.J. Braenden represented the United Nations and Miss E.S. Lumsden was the Executive Secretary of the Working Group.

6. It was noted that considerable progress had been made since the initiation of the research, particularly since the third Working Group.

7. Differences in growth habit, age at first flowering, and thebaine content were reported as these relate to genetic variations of P. bracteatum and to the wide range of ecological conditions under which the plant is being grown experimentally.

8. Consideration was given to methods of establishing stands whether by (a) direct seeding or seedling transplants or (b) vegetative reproduction by cuttings (longitudinal sections through root crown and upper root or transverse sections of root). The importance of high quality seed with good germination rate was recognized as an essential component of stand establishment. Consideration was also given to the effect of the depth of planting on seedling emergence 1/. Earlier experiments had shown that the best temperature range for germination of P. bracteatum seed was between 15 and 25°C 8/. This has since been confirmed at a number of locations. Maximum and minimum temperatures play an important role during the initial year of stand establishment. Temperatures of -10°C or below (without snow cover) and of +40°C or above killed unprotected plants. However, these young plants can be effectively protected from such temperature extremes by appropriate mulches or coverings.

1/ See document ST/SOA/SER.J/15, para 13.

8/ ibid, para 12.

9. The Group recognized the importance of evaluating plant spacing in terms of thebaine yield per unit area and consideration was given to spacing within and between rows. Some locations reported best results in terms of weed control and yield of capsules when plant density was high but it was recognized that optimum spacing may vary from location to location depending on such factors as available moisture, weed problems, methods of weed control and harvesting methods.

10. Broadcast seeding can be a simple approach to stand establishment but this may have disadvantages, particularly in connexion with weed control and the use of herbicides on the one hand and mechanical cultivation on the other. It was noted that, at the present time, there is no herbicide which adequately meets all requirements. However, reports indicated that Azulam [9] can be fairly effective when properly applied. Results of research on the use of the activated carbon method [10] of weed control were presented to the meeting. The report clearly demonstrated the potential of this method for establishing P. bracteatum seedlings from direct sowing. This method has been used successfully with other small seeded species.

11. There were several reports on the application of herbicides during the plant dormancy period. This can be done without detrimental effects on P. bracteatum. Paraquat [11] and diquat [12] had been used effectively during this period when there is no active growth taking place.

9/ Methyl sulfanilyl carbamate.

10/ The seeded rows are protected by a narrow band (about 5 cm) of activated carbon, then a general pre-emergence herbicide is applied over the entire surface of the field at the appropriate rate. The carbon deactivates the herbicide so that seedlings come up through the carbon undamaged.

11/ 1,1'-dimethyl-4,4'-dipyridinium dichloride (or methosulfate).

12/ 9,10-dihydro(8,10a)diazoniaphenanthrene dibromide.

12. It was generally agreed that P. bracteatum is a highly cross-pollinated species. The controlling mechanism appears to be self incompatibility either genetic or somatic, however, there is some evidence of a low level of self pollination.

13. The perennial nature of P. bracteatum was discussed and several reports confirmed that the productive life of this plant is at least eight years [13/]. In fact, there is experimental data indicating that yield of thebaine per plant increases with plant age.

14. Mention was made of the possibility of using seeds in paper strips to facilitate precision in plant spacing, and perhaps enhancing weed control and fertilizer application. Use of pelleted seed has met with mixed success.

15. Several participants reported on disease and insects attacking the various parts of the P. bracteatum plants. It was recognized that chemicals would control certain of these pests but the primary objective should be the development of disease and insect resistant varieties which would, at the same time, have high alkaloid yield.

16. The meeting was informed by several participants that the thebaine concentration in capsules varied with the stage of capsule maturity. It was generally agreed that the concentration reached a peak two to four weeks after flowering. Following this period of development, the percentage of thebaine decreased until just prior to capsule maturity when there was an additional accumulation of the alkaloid. It was also reported that a portion of the thebaine in the capsule is probably in a bound form in the post-flowering period. It was noted, however, that the bound form disappears and becomes part of the total thebaine prior to capsule maturity. Meconic acid was found to be present but probably not in the bound form.

13/ This was the longest period of controlled growth of any P. bracteatum stand.

17. Reports were presented on progress in selecting and breeding of P. bracteatum populations with high thebaine content and other desirable characteristics. Data were given showing the range of genetic variability within the species and the opportunities for plant improvement. The identification of plant selections from Arya II [14/] with high thebaine content was reported. In certain selections significant positive correlations were found between size of capsules and thebaine percentage. Experimental evidence was provided which indicates that thebaine content is a heritable characteristic. Also it was reported that the magnitude of variation in thebaine content of capsules was greater between plants than within plants.

18. It was noted that preliminary research was in progress in connexion with thebaine production through tissue culture. It was reported that, after the tenth generation, thebaine comprised 0.1% of the dry matter. These investigations include the study of various rhythms of culture in different types of environment, the analysis of mitotic activity and of the relationship within the cell between proliferation and biosynthesis. Studies were also being made on the production and selection of improved cell strains.

19. Preliminary data show that ^{14}C-labelled phenylalanine, tyrosine, glycine and urea when applied to capsule, leaf and stem surfaces of P. bracteatum

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14/ At the second Working Group on P. bracteatum considerable interest was expressed in new collections from the Mahabad region in the west of Iran. The capsules of these plants have the highest content of thebaine. The pigment and resin content is low and no other alkaloid was detected in the dry capsules. It was thus possible to obtain pure thebaine relatively easily. In view of the importance of this discovery, the second Working Group felt that it would be desirable to nomenclaturally distinguish collections of the Alborz Mountains from those of the Mahabad region by referring to the former as "Arya I" and to the latter as "Arya II". (see document ST/SOA/SER.J/2)

are absorbed and at least partially utilized in alkaloid biosynthesis. Radioactive thebaine was found primarily in the capsules of the plants treated with each of the four precursors. There was little radioactivity present in the extracts from the root stem transition zone or leaves. No radioactive compounds were found in the root. It was suggested that future experiments on biosynthesis of thebaine should include precursors with small molecules, in general not belonging to the primary metabolites.

20. The meeting was informed of the structure of articulated laticifer or latex cells in P. somniferum; similar structures were found in P. bracteatum. The latex cell contains numerous vesicles, organelles, ribosomes and a single nucleus. As these cells mature, thin areas develop in walls of contiguous cells. These thin areas become perforated so that the cells are interconnected and eventually, as more and more cells are connected, form an anastomozing system of latex vessels (articulated laticifers). They are derived from endoplasmic reticulum and usually develop a thickened area or cap prior to perforation of the latex cells. The vesicles represent the major component of exuded latex. It is not yet known whether the alkaloids are synthesized within the vesicle, on the vesicle membrane, within the cap or elsewhere in the latex cell.

21. The Group felt that suitable methods are now available for the determination of thebaine in P. bracteatum material. The reference samples prepared by the UN Laboratory had been analysed in various laboratories by the method recommended by the third Working Group [15] and the results obtained were in good agreement.

22. Several modifications of the method that had been recommended by the third Working Group were suggested [16]: freeze-drying of material had been found

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15/ See Annex II.

16/ These modifications will be described in a document to be issued in the ST/SOA/SER.J/.. series.

to give higher thebaine values than air-drying at 60°C and specification of the particle size of samples is necessary in order to obtain reproducible and comparable results. It was desirable to have uniform milling devices and procedures. The optimum temperature for extraction was 15°C or lower and continuous elution was of advantage. At the present time, gas-liquid chromatography seems the preferred technique but it was noted that promising results had been obtained with high pressure liquid chromatography.

23. The thebaine content of the dried ground capsules was relatively stable for a considerable time. However, if any oil was present from the seeds the amount of thebaine diminished fairly rapidly.

24. A pilot study had been carried out on 3.1 metric tons of Arya II capsules to determine the feasibility of commercial extraction of thebaine from P. bracteatum. No difficulties had been encountered with the process used.

25. Considerable interest was shown in the presentation of a review of methods for the conversion of thebaine into codeine and it was suggested that this review should be included in the report of the Group [17]. It was also noted that thebaine could be converted directly into hydrocodone and dihydrocodeine with high yield.

26. Information presented on the percentage of oil extracted from P. bracteatum seed by commercial type presses confirm the oil content of P. bracteatum seed reported to the third Working Group [18]. The oil and seed meal from a large scale (10 metric tons) pilot study are being evaluated for their food, feed and industrial values.

27. The Working Group was informed of a new alkaloid-producing perennial plant found at high elevations in Iran. It was reported to be similar to

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17/ See Annex III.

18/ See document ST/SOA/SER.J/15, Annex VI.

Papaver fugax and Papaver caucasicum in morphological characteristics. It was noted that a new name had been proposed but not published. Preliminary analyses show that all parts of the plant contain approximately 1% thebaine with small quantities of fugapavine and two or three other minor alkaloids. Thebaine constitutes 95% of the total alkaloid component and appears to be equally distributed throughout the plant. At the present time, there is no evidence that higher concentrations of alkaloid accumulate in the capsules as compared with other parts of the plant, as in P. bracteatum. The plant has a single stalk reaching 1½ to 2 metres in height on which is produced 50 to 100 small pink flowers. Although the capsules are very small, the brownish seeds are 3 to 4 times larger than those of P. bracteatum.

28. In summarizing its debate, the Group reviewed the results achieved since the inception of the project in December 1972. The meetings of the Working Group together with the rapid publication avenue provided by the United Nations Narcotics Laboratory had helped all concerned to focus resources on problem areas and to avoid unproductive lines of research and wasteful duplication of effort.

29. There had been significant achievements in several aspects of the research and development of P. bracteatum, particularly in connexion with:

- methods of cultivation;
- the determination of thebaine in P. bracteatum material;
- semi-industrial processing of seeds for oil and protein and extraction of thebaine from capsules.

30. However, further investigations are desirable in such fields as:

- control of weeds, pests and diseases;
- plant growth requirements (for example, nutrition, water, photo-period, thermo-periods, spacing);

- harvesting practices (with special reference to large scale production);
- pilot studies to determine the processing technologies needed for commercial production [19];
- breeding and selection;
- morphological and anatomical studies relating to biosynthesis, translocation and metabolism of thebaine (including precursor studies for yield improvement).

31. The Group agreed that it would be highly desirable and extremely useful if the United Nations Narcotics Laboratory were to continue its leadership role in coordinating the research on P. bracteatum and that it should determine how this coordination can be most effectively carried out in the future.

32. Appreciation was expressed on the part of the observers for the opportunity to participate in the meetings of the Working Group [20]. The Group also recorded its appreciation of the visits that had been arranged to experimental cultivations of P. bracteatum.

33. Dr. C. Vaille, Inspector General of Social Affairs and Representative of France on the Commission on Narcotic Drugs and Mr. T. Francfort, Chief of the Narcotics Bureau of the French Ministry of Public Health, participated in the closing session of the meeting. Dr. Vaille underlined the concern at the international level in ensuring adequate supplies of codeine for medical purposes while, at the same time, avoiding over-production. The Commission on Narcotic Drugs was therefore especially interested in the research on P. bracteatum. In commending the results being achieved Dr. Vaille credited much of the progress to the close international collaboration as exemplified by this and previous meetings of the Working Group.

19/ A preliminary pilot study has indicated that this technology may be of an order of complexity similar to that for poppy straw but further data are necessary.

20/ See Annex IV.

ANNEX I

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Miss M.S. Lumsden

Dr. J.-L. Ibañez-Martin

Mrs. I. Bouthiaux (Administrative Assistant to the Group)

ANNEX II

At the third Working Group on Papaver bracteatum it was recommended that the following method be used for the determination of thebaine */:

1. Drying of Plant Tissue:

It was recommended that plant tissue be oven dried at 60°C to a constant weight as soon as possible following collection. Several members took exception to this procedure noting that thebaine may be lost using this protocol and that freeze-drying of samples would possibly be better. However, not all members had access to freeze-drying equipment. It was suggested that tissue be cut-up to facilitate oven drying, especially root tissue.

2. Particle Size:

It was recommended that samples be powdered so that all the sample passes through a 0.5 mm mesh and is thoroughly mixed immediately before weighing for analysis. Weight correction due to hygroscopic water absorption should be made by heating a small portion to 105°C and re-weighing at the time of analysis.

3. Sample Size for Analysis:

It was recommended that 0.1 to 0.5 grams of sample be used in analyses.

4. Extraction Solvent:

Acetic acid (5%) was suggested as the extraction solvent but would be considered tentative until fully evaluated by the members.

5. Procedure:

(a) Samples should be agitated for 30 minutes in 25 ml of acetic acid (5%) solution. It was recommended that shorter or longer agitating times be evaluated for efficacy of extraction technique.

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*/ See document ST/SOA/SER.J/15, Annex V.

(b) Filter eluent through a sintered glass funnel and repeat extraction two further times. Combine the filtrates.

(c) Add 25 ml of $CHCl_3$ and adjust the pH of the aqueous phase to pH 9.5-10 with concentrated NH_4OH with agitation. Separate $CHCl_3$ phases.

(d) Repeat extraction of the aqueous phase with one 25 ml portion of $CHCl_3$ followed by two 15 ml portions of the same solvent.

(e) Combine the $CHCl_3$ phases and evaporate to dryness preferably *in vacuo* at 40°C.

(f) To the flask containing the residue, add a known volume of ethanol containing an appropriate quantity of internal standard. Suggested internal standards include tetrahydrothebaine, cholesterol acetate, antipyrine and laudanosine. Use of one or more internal standards may be appropriate for certain analytical applications.

6. Gas-liquid Chromatography:

It was recommended that deactivated glass columns or glass-lined steel columns be used to avoid decomposition of thebaine (via metal catalysis). It was suggested that the columns be packed with 100/120 mesh Gas Chrom Q coated with 2-3% OV-17 liquid phase or their equivalents. Suggested operating temperatures should range between 260-280°C with either nitrogen or helium as carrier gas.

7. Results:

Results should be calculated on the basis of moisture-free content of plant tissue after drying at 105°C */.

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*/ Thebaine standardization: check the purity of the standard thebaine by determining the $E_{1\ \text{percent, 1 cm}}$ in 0.1N HCl at 285 nm or at the λ max.

ANNEX III

CONVERSION OF THEBAINE INTO CODEINE

by François Krausz

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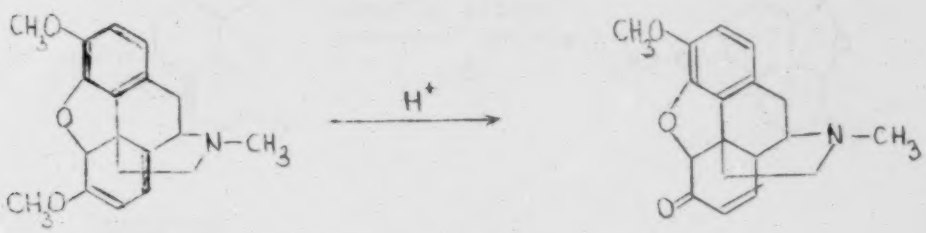
The need for converting thebaine into codeine first became apparent in the search for ways of making profitable use of thebaine, a by-product which is obtained in considerable quantities during the separation of the alkaloids of opium. The fairly recent discovery of a thebaine poppy, Papaver bracteatum, further emphasized the need for such a process. From the outset, it was logical to assume that the process would involve codeinone as an intermediate.

At the beginning of this century, Knorr and Hörlein observed that thebaine, when treated with dilute sulphuric acid, produces a highly complex mixture, from which it is possible to isolate codeinone, with a very low yield (figure 1).

FIGURE 1



THEBAINE CODEINONE

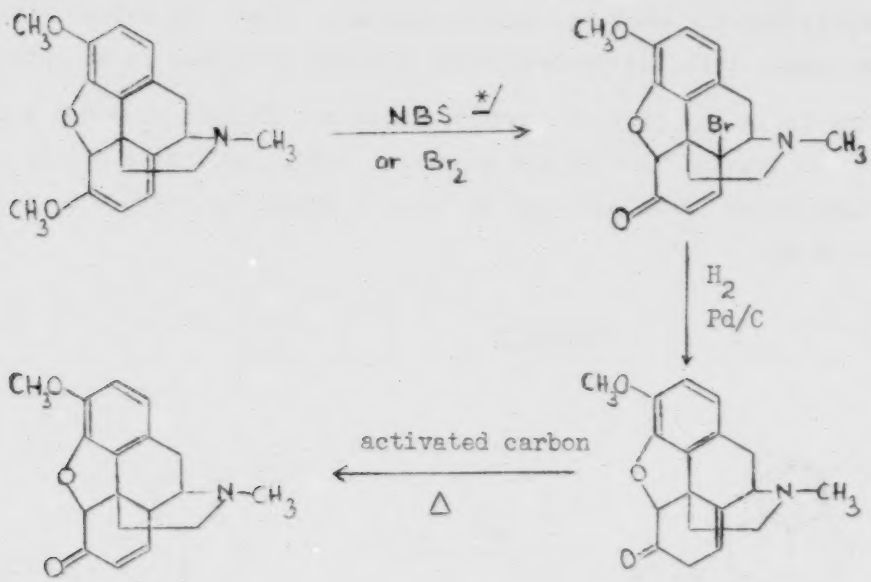
Knorr, Hörlein, Ber. (1906), 39, 1409
Schöpf, Hirsch, Ann. (1931), 489, 224

This discovery was of great theoretical importance since it shed some light on the relationships between the alkaloids of opium; but its practical value was nil because yields were low and isolation was difficult.

Also, the first practical method of reducing codeinone to codeine was not elaborated until the 1950s.

Great progress in the conversion of thebaine into codeinone was achieved in the work of Conroy (figure 2)

FIGURE 2



NEOPINONE

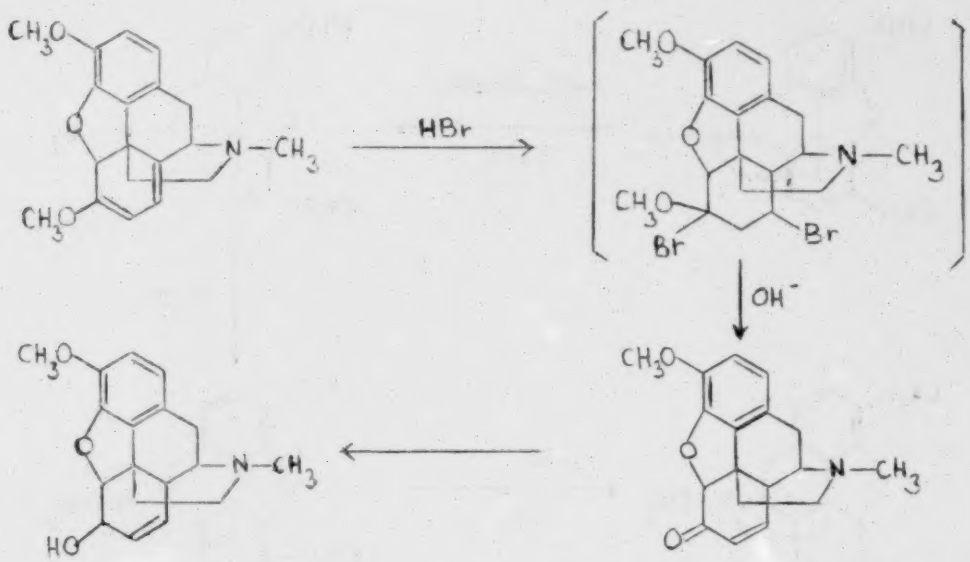
Conroy, J. Amer. Chem. Soc. (1955), 77, 5960
Krausz, Rüll. Bull. Soc. Chim. (1960), 2148

*/ N-bromosuccinimide

who discovered a clean method of converting thebaine into 14-bromocodeinone; this substance, when subjected to catalytic hydrogenation, was converted into neopinone, which itself isomerizes under various conditions into the conjugated ketone, codeinone. The total yield is about 37 per cent. However, the extension of this method to yield quantities larger than those produced under laboratory conditions would seem rather disappointing.

Our reflexions on the development of the chemistry of thebaine led us, at the beginning of the 1960s, to elaborate an extremely simple method of converting thebaine into codeinone (figure 3).

FIGURE 3



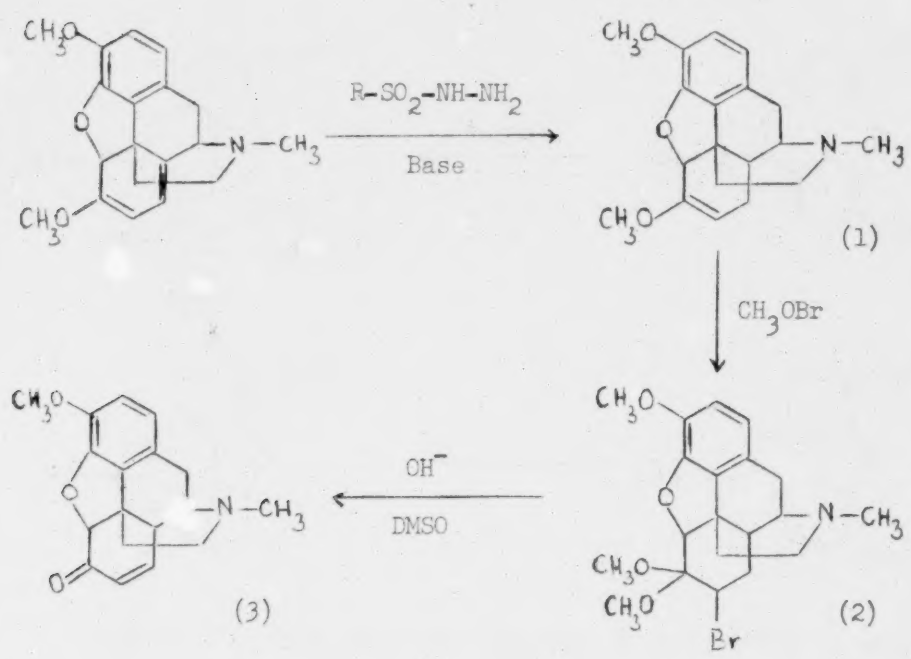
CODEINONE: SEPA (inv. F. Krausz), Fr. pat. 1.290 174 (1961)
Gavard, Krausz, Rüll, Bull. Soc. Chim. (1965) 486

CODEINE: Merck (inv. M. Gates), Fr. pat. 1.103 238 (1955)
Krausz, Gavard, C.R. Acad. Sc. (1962) 254, 3101

When treated with hydrobromic acid in an anhydrous medium, thebaine, after hydrolysis, produces codeinone in a single step (the intermediate product, which is shown in brackets is not isolated) and with very satisfactory yields and purity. After the codeinone has been reduced to codeine, the overall yield from the conversion of thebaine into codeine is of the order of 70 per cent.

Very recently, we noted an ingenious method of converting thebaine into codeine, which is illustrated in figure 4.

FIGURE 4



(1) Eppenberger, Warren, Rapoport, Helv. Chim. Acta (1968) 51, 393
Macfarlan Smith Ltd., Fr. pat. 2.117 924 (1972)
(2) Rapoport, Lovell, Reist, Warren (1967), 89, 1942
(3) Macfarlan Smith Ltd., Belg. pat. 827 568 (1975)

The use of aryl sulfonyl hydrazide makes it possible to produce the diimine HN = NH, which was first used by Rapoport et al., in the reaction medium reasonably safely. The thebaine is reduced to dihydrothebaine, with excellent yields. The latter, upon reaction with CH_3OBr, is converted into 7-bromoacetal dihydrocodeinone (ref.2). From this bromoacetal using sodium or potassium in a DMSO medium, it is possible to obtain codeinone acetal, from which codeinone is obtained by acid hydrolysis.

This ingenious series of reactions produces interesting yields. However, in view of the relative complexity of the operations and the cost of some of the raw materials, we believe that conversion by the process described earlier would be more economical.

ANNEX IV

Statement made by Mr. Clealand Baker on behalf of representatives of manufacturing companies present as observers

As a representative of a pharmaceutical manufacturer that uses a large quantity of codeine in formulating medicinal products, I have appreciated the privilege of attending the last two U.N. Papaver bracteatum meetings as an observer. I have been impressed with the fine cooperation of the Working Group members, and the effective coordination of the studies by the U.N. Laboratory under Dr. Braenden's direction.

The report given at this meeting covering the results of the chemical analysis of the reference samples of P. bracteatum capsules for thebaine content, is a good example of the productive value of these coordinated studies. I know of no similar scientific development project that has moved along this rapidly, which may emphasize the importance of the effective U.N. Laboratory coordination of this international study group involving scientists from government, academia, and industry. I hope this fine cooperation will continue in future studies that are done on this plant.

P. bracteatum has the potential to contribute substantially to the world community in several ways - to improve the raw material supply for codeine, to stabilize or possibly reduce the rapidly rising price of codeine, and by providing a raw material source that is free of naturally occurring morphine, to be useful in reducing the drug abuse potential from the alkaloid source.

I wish to congratulate the U.N. Laboratory and the Working Group on their achievements, and also Dr. Morice, as President of the Conference, for his fine conduct of the meetings. My appreciation also to Mr. Dumont and Mr. Candillon for their hospitality during the Conference.